REMARKS

The Applicant thanks the Examiner and his supervisor for the courtesy of a telephone interview on 7 July 2005. At that time, various aspects of the claims were discussed, and the Examiner expressed concern with respect to the apparently variable use of the term "VH" in the art. In the interests of clarity, the applicant has amended "VHs" in claim 25 to read "conventional variable heavy domains". Support for this phasing can be found, *inter alia,* on page 14, line 28 of the application as filed.

Claims 25 to 28 are currently under consideration.

Claim 25 is directed to a camelid cDNA library...coding for antigen-binding fragments of conventional variable heavy domains of camelid llama antibodies.

For the reasons which follow, the applicant submits that the cited art fails to teach a library encoding such VH fragments. In fact, the cited art is directed to VHH antibody fragments and related libraries.

A technical discussion of the differences between conventional variable heavy domains (VH) and VHH fragments follows, which the applicant hopes will prove useful to the Examiner.

Conventional (or classical antibodies) found throughout the vertebrate phylum have the common basic structure shown in **Fig. 1A**. They consist of two identical heavy (H) chains and two identical light (L) chains. The H chain consists of one variable domain (V) and three constant domains (C). The L chain consists of one variable domain (V) and one constant domain (C). The C domains that are part of the H chain are designated C_H (i.e., C_H1, C_H2 and C_H3) and the C domain that is part of the L chain is designated C_L. Similarly, the V domain that is part of the H chain is designated V_H and the V domain that is part of the L chain is designated V_L. V_H plus V_L together form the

antigen binding structure. Not shown in the figure is the hinge region which connects the C_H1 to C_H2.

A fundamentally different kind of antibodies referred to as heavy chain antibodies (HCAs, **Fig. 1B**) were discovered in 1993 in the sera of llamas and camels. They are different from conventional antibodies with respect to the following:

1. They lack the equivalent of the L chain in conventional antibodies, consist of two identical H chains and thus are referred to as HCAs;
2. Their heavy chains lack the equivalent of a C_H1 domain in conventional antibodies;
3. Their variable domain (V_HH, see below) is fundamentally different from its V_H counterpart in conventional antibodies and
4. Their hinge has a different structure, connects V to C_H2, compared to connecting C_H1 to C_H2 in conventional antibodies, and is short or long.

As a result of lack of a L chain, the antigen binding structure in HCAs is formed by one variable domain which is part of the H chain. It is referred to as V_HH (a $\underline{V_H}$ from a $\underline{H}$CAs). However, although very rarely, the abbreviation V_H, typically reserved for V domains that are part of the H chains of conventional antibodies, has been used to describe the V domains of HCAs (e.g., Frenken WO99/37681 and US 6,399,763). However, in such instances, the designation V_H only means that the variable domain is attached to a heavy chain and should not be extended to mean that the HCA V_Hs (i.e., V_HHs) are the same as the V_Hs from the conventional antibodies; far from that, V_Hs and V_HHs are <u>fundamentally different</u> from each other. During the course of evolution, V_HHs have acquired fundamental structural changes, through known and unknown mutations, which have made them distinct from conventional V_Hs both in terms of biophysical properties and antigen recognition mechanism:

1. V_H contribution to antigen binding and recognition requires its association with V_L; ordinarily it is not functional in the absence of the V_L. This is not only true of whole antibodies but also of smaller recombinant derivatives such as Fabs, scFvs and Fvs (**Fig. 1A**). A V_HH, on the other hand, is an independent domain and forms a functional antigen binding structure on its own.
2. Likely to compensate for the absence of V_Ls, which contribute significantly to the diversity of the conventional antibody repertoire for antigen recognition, V_HHs have evolved to have (i) larger overall variability throughout their sequences, (ii) longer CDR1 and CDR3 (CDRs in V domains are primarily involved in antigen binding), (iii) extra disulfide linkages connecting CDR3 to CDR1 or CDR2 and (iv) new antigen binding loop canonical structures.
3. In isolation, away from its V_L partner, a V_H will typically form aggregates in solution, whereas V_HHs are highly soluble. V_HHs also have high chemical and thermal stabilities, high refolding efficiencies and are resistance to digestion by proteases.

Thus, to reiterate, the fact that for example Frenken et al. have used "V_H" to designate the heavy chain variable domains in both conventional and heavy-chain antibodies simply reflects the fact that in both cases the variable domain, V, is attached to the heavy chain, H. The same nomenclature approach has been observed in the case of shark IgNARs (Immunoglobuling nurse shark antigen receptor). Similar to camelid HCAs, IgNARs also lack light chains. They are, however, significantly different from HCAs and show even more departure from conventional antibodies.

Thus, the Applicant submits that conventional heavy chains domains (VHs) are different from VHHs as described in the cited art.

In light of the forgoing, the applicant submits that this application is in condition for allowance. Prompt and favourable action is respectfully requested.

Respectfully submitted,

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I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Margaret McKay — October 3, 2005